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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/980,548	03/27/2002	Peter Mueller	930008-2008	5730

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FROMMER LAWRENCE & HAUG
745 FIFTH AVENUE- 10TH FL.
NEW YORK, NY 10151

EXAMINER	
MCKELVEY, TERRY ALAN	
ART UNIT	PAPER NUMBER
1636	6

DATE MAILED: 03/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/980,548	MUELLER ET AL.	
	Examiner	Art Unit	
	Terry A. McKelvey	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Specification

The disclosure is objected to because of the following informalities:

1. The specification improperly refers to claims (for example, at several locations on page 5). Because the claims can change or be canceled as a result of prosecution, what is included in the specification at that location would be either incorrect or improperly changed. No reference to specific claims is permitted in the specification.

2. The specification lacks the required Brief Description of the Drawings that is required, for Figure 1, at least. It is unclear whether the figure descriptions at pages 9-15 are intended to be brief descriptions of figures 2-13, but if they are, they should not be interrupted by additional text, such as at page 14, first full paragraph, and the second half of page 9. A complete, uninterrupted Brief Description of the Drawings is required.

Appropriate correction is required.

Claim Objections

Claims 1-4 are objected to because of the following informalities: because claims are only properly written in complete sentences, the lack of the proper articles "A" or "An" at the front of each claim results in a grammatically incorrect sentence. Also, the claim section should begin with the first part of the sentence such as "We claim:". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a promoter construct comprising MPSV enhancer repeats of a specific sequence or isofunctional

variants of thereof obtained by substitution, insertion, or deletion of one or more nucleotides, IRF-1 binding sites of a specific sequence or isofunctional variants of thereof obtained by substitution, insertion, or deletion of one or more nucleotides, and CMV minimal promoter of a specific sequence or isofunctional variants of thereof obtained by substitution, insertion, or deletion of one or more nucleotides.

These claims, including claim 4 which is drawn to use of an expression vector comprising the promoter construct, are genus claims because they comprise three different elements (parts of the promoter construct sequence) each of which constitutes a genus: the isofunctional MPSV enhancer repeats, the isofunctional IRF-1 binding sites, and the isofunctional CMV minimal promoter. Thus, these different sequences encompass many different nucleotide sequences having one or more nucleotide substitutions, deletions, insertions, and/or additions to the single sequence for each element, SEQ ID NOS:1-3 respectively, described by the specification.

The specification and claims do not indicate what distinguishing structural attributes are shared by the genus members of each of the three elements. The specification and claims do not place any limit on the number of nucleotide substitutions, deletions, insertions, and/or additions that may

be made to each of the three different sequences. Thus, the scope of the claims includes numerous structural variants of the three sequences in the claimed promoter construct, and the genus is highly variant because a significant number of structural differences between the genus members is permitted. Although these types of changes are routinely done in the art, the specification and claims do not provide any description as to what changes can or should be made. Structural features that could distinguish specific sequences in the each element genus from others in the nucleic acid class are missing from the disclosure. No common structural attributes identify members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common structural attributes or characteristics that identify the members of each genus, and because the members of each genus are highly variant, the single sequence of each element of the promoter construct referred to in the specification (SEQ ID NOS:1-3) is insufficient to describe the genus drawn to including isofunctional variants of each sequence. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of

species to describe the genus. Thus, applicant was not in possession of the claimed genus.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 1, the use of "fusion protein comprising IRF-1 and the estrogen receptor" renders the claims vague and indefinite because it appears from the specification and the art that the fusion protein is between IRF-1 and the hormone binding domain of the estrogen receptor, not a fusion protein comprising the IRF-1 and the entire estrogen receptor.

Regarding claim 2, the use of "Expression vector(s)" renders the claim vague and indefinite because it is unclear how many vectors are encompassed by "vector(s)". Claimed products are properly claimed in the singular form, e.g., "An expression vector", instead of the unclear plural. Also, the use of "a promoter construct and/or a transactivator construct according

to claim 2" renders the claim vague and indefinite because claim 1 is drawn to a promoter-transactivator system, not a promoter construct or a transactivator construct (which are only parts of the claim). (Dependence on another claim is only proper when the entire claim is referred to, not parts only.)

Regarding claim 3, the use of "Mammalian cells" renders the claim vague and indefinite because it is unclear how many cells are encompassed by "cells". Claimed products are properly claimed in the singular form, e.g., "A mammalian cell", instead of the unclear plural.

Regarding claim 4, the use of "culturing said mammalian cells, or transfected or transformed mammalian cells according to the expression vectors(s) of claim 2" renders the claim vague and indefinite because it is unclear how to culture "according" to expression vectors. Also, the distinction between "said mammalian cells, or transfected or transformed mammalian cells" is unclear because the step appears to rely upon the previous transfecting or transforming step and thus shouldn't be directed to the non-transfected or transformed cells as indicated in the first part of the phrase. Finally, the use of "suitable medium" renders the claim vague and indefinite because the metes and bounds of what constitutes "suitable" in this context are unclear. Also, it should be noted that correction of claim 2

also requires the corresponding correction of claim 4 to refer to the singular form.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kirchhoff et al in view of Von Hoegen et al (WO 98/11241).

Kirchhoff et al teach a conditional expression system comprising a cell comprising an expression vector comprising an IRF-1 binding site (corresponds to SEQ ID NO:2) operably linked upstream of a heterologous promoter and an expression vector which expresses a fusion protein composed of IRF-1 and the hormone binding domain of the estrogen receptor. The expression system allows to control gradually the growth of mammalian cell lines by adjusting the intracellular concentration of active IRF-1 via estradiol in the medium (abstract; page 151, column 2-page 152, column 1). The productivity of the secreted protein which is controlled by the IRF-1 inducible promoter is strongly enhanced by estradiol (abstract). The reference teaches a process of inducible expression comprising transfecting or transforming mammalian cells with the expression vectors and culturing the resulting cell in a medium containing estradiol which induces expression of a gene operably linked to the IRF-1 controlled promoter (with estradiol also controlling the growth of the cells) (abstract; page 149, column 1 - page 151, column 2). The transcriptional activating capacity of the IRF-1 during proliferation induction is fully functional (page 152, column

1). Kirchhoff et al also teach: "In the pilot experiment (Figure 5) we show that making use of an inducible IRF-promoter production of a secreted protein can be significantly stimulated (about tenfold) by IRF-1 activation. This motivated us to construct strong constitutive promoters which are further activated by IRF-1 and by this can overcome the negative effect on productivity." (page 154, column 2).

Kirchhoff et al do not specifically teach the MPSV enhancer/CMV minimal promoter as the promoter that the IRF-1 binding site is operably linked to in the expression system taught by the reference.

Von Hoegen et al teach a preferred expression system comprising the MPSV enhancer sequence (corresponds to SEQ ID NO:1) upstream of a minimal CMV promoter (corresponds to SEQ ID NO:3) operably linked to a heterologous gene (page 10, lines 12-14; page 19, lines 20-21, 25-27; page 24, lines 13-19). This reference teaches that the MPSV enhancer/CMV promoter is strong and produces an excellent yield of proteins (encoded by the operably linked structural gene sequence) (abstract; page 19, lines 20-27).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to replace the heterologous promoter used in the IRF-1 binding

site/heterologous promoter expression system taught by Kirchhoff et al with the strong MSPV enhancer/minimal CMV promoter taught by Von Hoegen et al because Kirchhoff et al teach that it is within the ordinary skill in the art to operably link the IRF-1 binding site to a heterologous promoter to result in an IRF-1 inducible promoter which, when combined with the other element of the expression system taught by Kirchhoff et al (an expression vector which codes for a fusion protein comprising IRF-1 and the hormone binding domain of estrogen receptor), results in an expression system and method that is regulatable by estradiol (which also regulates the growth of the resulting cells), and Von Hoegen et al teach that it is within the ordinary skill in the art to use an MPSV enhancer/CMV promoter as a strong promoter for expressing heterologous genes.

One would have been motivated to do so for the expected benefit of replacing the weaker promoter used in the expression system taught by Kirchhoff et al, which is taught as being responsible for a negative effect on productivity, with a very strong promoter taught by Von Hoegen et al to result in a strong constitutive promoter that can be further activated by IRF-1, as taught by Kirchhoff et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been

a reasonable expectation of success to result in the claimed invention.

Regarding the location of the IRF-1 binding site between the MPSV enhancer and the CMV promoter, it would have been obvious to place the IRF-1 binding site at that location because the IRF-1 binding site is taught in Kirchhoff et al as being upstream of the heterologous promoter, and it is and was within the ordinary skill and practice in the art to locate enhancer sequences upstream of the entire promoter sequence, including promoter elements that regulate the minimal promoter, such as, in this case, IRF-1 binding site.

Conclusion

No claims are allowed.

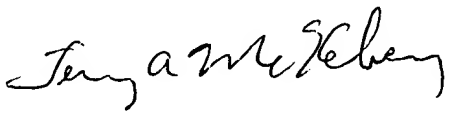
Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's

representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning rejections or other major issues in this communication or earlier communications from the examiner should be directed to Terry A. McKelvey whose telephone number is (703) 305-7213. The examiner can normally be reached on Monday through Friday, except for Wednesdays, from about 7:30 AM to about 6:00 PM. A phone message left at this number will be responded to as soon as possible (i.e., shortly after the examiner returns to his office).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached on (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.



Terry A. McKelvey, Ph.D.
Primary Examiner
Art Unit 1636

March 24, 2003